Long-Term Surveillance of Ground-Glass Nodules
Evidence from the MILD Trial

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Introduction: The purpose of this study was to evaluate the natural evolution of ground-glass nodules (GGNs) in the Multicentric Italian Lung Detection (MILD) trial, which adopted a nonsurgical approach to this subset of lesions.

Methods: From September 2005 to August 2007, 56 consecutive MILD participants with 76 GGNs were identified from 1866 individuals who underwent baseline low-dose computed tomography. The features of GGNs were assessed and compared with the corresponding repeat low-dose computed tomographies after a mean time of 50.26 ± 7.3 months. The GGNs were classified as pure (pGGN) or part-solid (psGGN) GGNs. The average of the maximum and the minimum diameters for both pGGNs and psGGNs and the maximum diameter of the solid portion of psGGNs were manually measured. At follow-up, GGNs were classified as follows: resolved, decreased, stable, or progressed (according to three defined growth patterns).

Results: A total of 15 of 48 pGGNs (31.3%) resolved, 4 of 48 (8.3%) decreased in size, 21 of 48 (43.8%) remained stable, and 8 of 48 (16.7%) progressed. Among the psGGNs with a solid component smaller than 5 mm, 3 of 26 (11.5%) resolved, 11 of 26 (42.3%) remained stable, and 12 of 26 (46.2%) progressed. One of the two psGGNs with a solid component larger than 5 mm remained stable, and the other decreased in size. Four lung cancers were detected among the GGN subjects, but only one arose from a psGGN, and was resected in stage Ia.

Conclusions: The progression rate of the GGNs toward clinically relevant disease was extremely low in the MILD trial and supports an active surveillance attitude.

Key Words: Ground-glass nodule, Lung cancer screening, Long-term surveillance.

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Subsolid lung nodules, also termed ground-glass nodules (GGNs), are often encountered during computed tomography (CT) examinations for lung disease. They may represent a variety of disorders ranging from inflammatory abnormalities to lung neoplasms, and may indeed show different evolution over time.[1–3] If it is true that some GGNs may be stable over time and more likely represent malignant or premalignant abnormality, a substantial proportion of them are instead transient.[4–6] Indeed, despite the increased understanding during the last decade of the varieties of the GGNs, these lesions continue to represent a challenging task for clinicians, surgeons, and radiologists.

The difficulty in the management of the GGNs is particularly evident in the lung cancer screening setting, partly because of the scarce information on these entities at the time in which multicentric randomized trials were designed.[7,8] Furthermore, there are important data consistent with the notion of overdiagnosis occurring in a considerable percentage of screening-detected lesions.[9–11] However, the nonuniform management strategies for these lesions across the lung cancer screening trials may give the possibility of achieving additional important information in this regard.

Thus, the purpose of this study was to evaluate the evolution of the GGNs in the Multicentric Italian Lung Detection (MILD) trial, which adopted a very conservative, nonsurgical approach to this subset of lesions.

PATIENTS AND METHODS

Study Population

The study population comprised all the consecutive patients who underwent baseline low-dose (LD) CT (LDCT) examination between September 2005 and August 2007 (n = 1866, 1280 men, 68.6%, and 586 women, 31.4%; mean age 57.6 ± 4.8 years) as part of the MILD project at the National Cancer Institute of Milan. The MILD project is an ongoing multicentric population-based randomized, controlled, lung cancer screening trial, and its primary aim is the impact of early lung cancer detection on mortality. The MILD project was approved by the Institutional Review Boards, and written informed consent was obtained from all participants. For this substudy, the original Institutional Review Boards' approval and informed consent allowed use of data for future research.

Part of the study subjects had been included in other studies addressing a separate hypothesis.[12,13] Eligibility criteria for the MILD included: 49 to 75 years of age, current or former smokers (having quit smoking within 10 years before recruitment) with at least 20 pack-years of smoking history and no history of cancer within the previous 5 years. Details of MILD eligibility criteria, randomization protocol, lung nodule detection, and management protocol have been previously described.[12]

LDCT Technique

LDCT was performed by using a 16-detector row CT scanner (Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany). All LDCT scans of the whole lung were acquired during one deep inspiratory breath-hold without the use of the contrast medium. Standard LDCT parameters were as follows: 120 kV, effective 30 mAs, individual detector collimation 0.75 mm, gantry rotation time 0.5 second, pitch 1.5. LDCT images for the lung nodule detection were reconstructed as follows: 1-mm–thick sections with a reconstruction increment of 1 mm (medium-sharp kernel - B50f).

Original MILD Management of the GGNs

Using defined criteria, radiologists working for the MILD trial (MILD readers) were asked to report the presence of any pure (pGGN) and part-solid (psGGN) GGNs. According to the MILD protocol, both pGGNs and psGGNs with a solid component smaller than 5 mm had to be followed up regardless of their size and their number (i.e., single or multiple). These subjects were scheduled for repeat LDCT scanning according to both their LDCT arm of randomization and other lung findings.[12] Only the psGGNs with a solid component larger than 5 mm were considered suspicious for malignancy and indeed followed up at 1 year (if sized 5 to 8 mm) or evaluated by positron emission tomography (PET) scanning and invasive diagnostic procedures (if sized more than 8 mm) as jointly established by the senior MILD radiologist (AM) and the thoracic surgeon (UP) coordinating the MILD trial.

Radiologic Assessment of the GGNs by Core Readers

For the present study, all the LDCTs were reviewed on three different personal computers running a Dicom viewer software validated for clinical purpose (OsiriX, 3.5.1 Imaging Processing Software, 64-bit format, Pixmeo SARL, Bernex, Switzerland) by three readers (*core readers)* as follows: MS, CM, and GN reviewed 1203, 483, and 200 LDCT scans, respectively. The core readers were in the course of their training as thoracic radiology subspecialists at the Academic Hospital of Parma and they had 2 years' experience in interpreting thin-section CT scans. The core readers were blinded to the original interpretations by the MILD readers. They received specific training, which consisted of viewing a slide presentation that defined and showed examples of lesions having various features and understanding the current literature.

In cases of uncertain diagnosis, the core readers were instructed to classify the corresponding LDCT findings as positive, because these would have to be reviewed with a chest radiologist (NS with 5 years of experience in interpreting LDCTs lung cancer screening) who would then decide to maintain or discard the evaluations of the core readers. Subsequently, the core readers and the chest radiologist jointly classified each selected GGN as pGGN or psGGN.

Both baseline and the latest corresponding follow-up LDCT were evaluated for the GGNs measurements only by one of the three core readers (MS). For the pGGNs, both the maximum length and the width (defined as the longest diameter perpendicular to length on the same CT image) were measured. The GGN size was defined as the average of these two measurements.[14] For the psGGNs, the maximum length of the solid component was also measured. Measurements were manually determined using the electronic caliper. All these measurements were also repeated after 4 months by another core reader (CM) to evaluate the interobserver variability. Then, the core readers, the chest radiologist, and one thoracic surgeon coordinating the MILD trial reviewed in consensus both the baseline and the latest follow-up LDCT images to evaluate any change in attenuation (e.g., development of any solid component within a pure GGN) of the GGNs.

Data Analysis

At follow-up LDCT, each pGGN was classified as follows: resolved, decreased (by at least 2 mm as compared with the same nodule at baseline LDCT), stable, or increased (by at least 2 mm as compared with the same nodule at baseline LDCT). The development of a solid component within a pGGN was also considered a sign of progression/malignancy. Similar criteria were applied to psGGNs as follows: decreased (if the solid component alone or along with the total average size by at least 2 mm as compared with the same nodule at baseline LDCT), stable (including no variation of the solid component associated with a decrease of the total average size), and increased. The increase of the GGNs was subclassified into three growth patterns: (1) an increase by at least 2 mm of the solid component (Fig. 1*A*); (2) an increase by at least 2 mm of the total average size (Fig. 1*B*); and (3) an increase of both the solid component and total average size of at least 2 mm (Fig. 1*C*). The 2-mm threshold was based on intraobserver variation data reported by a prior study.[15]

Evolution of the GGNs was stratified either by the MILD original classification system (i.e., pGGNs, psGGNs with a solid component < 5 mm, and psGGNs with a solid component > 5 mm) or by the interim guidelines proposed by Godoy et al.[8] as follows: solitary pGGNs with the maximum diameter smaller than 5 mm, solitary pGGNs between 5 and 9 mm, solitary pGGNs larger than 10 mm, solitary psGGNs of any size, and multiple GGNs. To determine variability, we calculated the 95% confidence interval (CI) for the limits of agreement by using Bland-Altman analysis.[16] Normally distributed data are shown as means ± SD. p Values of less than 0.05 were considered to indicate statistical significance.